



Association Between Fasting Glucose Variability in Young Adulthood and the Progression of Coronary Artery Calcification in Middle Age

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OBJECTIVE

To investigate whether intraindividual variability of fasting glucose (FG) in young adulthood is associated with coronary artery calcification (CAC) progression in middle age.

RESEARCH DESIGN AND METHODS

We included 2,256 CARDIA (Coronary Artery Risk Development Study in Young Adults) participants with CAC assessment by computed tomography scanner at baseline (2000–2001) and 10 years later (2010–2011). CAC progression was assessed for each individual as the difference of logarithmic CAC scores at follow-up and baseline ($\log[\text{CAC (follow-up)} + 1] - \log[\text{CAC (baseline)} + 1]$). FG variability was defined by the coefficient of variation about the mean FG (FG-CV), the SD of FG (FG-SD), and the average real variability of FG (FG-ARV) during the 10-year follow-up. We investigated the association between FG variability and CAC progression with adjustment for demographics, clinical risk factors, mean FG level, change in FG level, diabetes incidence, and medication use.

RESULTS

After multivariable adjustment, 1-SD increment in FG-CV was associated with worse progression of CAC as demonstrated as percent change in CAC, with incident CAC 5.9% (95% CI 1.0, 10.7) and any CAC progression 6.7% (95% CI 2.3, 11.1) during 10 years. Similar findings were also observed in FG-SD and FG-ARV.

CONCLUSIONS

Higher FG variability during young adulthood was associated with greater CAC progression in middle age, suggesting its value in predicting risk for subclinical coronary artery diseases.

Individuals with diabetes have at least a twofold increased risk of cardiovascular events compared with those without diabetes, and cardiovascular events are the leading cause of diabetes-related morbidity and mortality (1–3). Coronary artery calcification (CAC), a noninvasive marker of subclinical atherosclerosis, has been identified to be an independent predictor of cardiovascular events (4–7). The American Diabetes Association recommends CAC screening as cardiovascular risk assessment in adults with diabetes ≥ 40 years of age (8). Due to the rapidly increasing

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prevalence of prediabetes and diabetes worldwide, there is an urgent need to understand the impact of diabetes-related factors on cardiovascular structure and function in the early disease process (9).

Recent epidemiological evidence suggests that greater long-term variability in plasma glucose is associated with higher risk for cardiovascular events among individual with diabetes (10–13). Whether this association is attributable to the increase of average plasma glucose level, variability due to diabetes medication use, or other cumulative risk factors is unclear. Moreover, the association between glucose variability and CAC has not been reported. Investigating the contribution of variability of glucose among young adults and adults in early middle age without diabetes may advance our understanding of how dysfunction in glucose homeostasis impacts CAC progression, a subclinical cardiovascular disease in early life. Our objective was to examine the prospective association of fasting glucose (FG) variability with 10-year CAC progression. We hypothesized that greater FG variability during young adulthood would be associated with advanced CAC progression by middle age.

RESEARCH DESIGN AND METHODS

Study Population

The Coronary Artery Risk Development Study in Young Adults (CARDIA) is a multicenter prospective investigation of 5,115 healthy young adults aged 18–30 years recruited in 1985–1986 from four U.S. metropolitan communities. A detailed design of CARDIA has previously been published (14). Participants are invited to participate in follow-up examinations approximately every 2–5 years. In this current study, data from follow-up examinations at CARDIA years 15 (2000–2001), 20 (2005–2006), and 25 (2010–2011) were collected. Participant retention rate was 74%, 72%, and 72% at year 15, 20, and 25, respectively, of the surviving participants. All participants provided written informed consent at each examination, and the institutional review board at each study site and coordinating center approved the study procedure for all examinations.

For our analysis, we excluded participants who did not have information for any of the CAC assessments at years

15 and 25 ($n = 456$) or had fewer than three valid FG values from year 15 to year 25 exams ($n = 786$). The final sample size for the analysis of any CAC progression was 2,256 participants (Supplementary Fig. 1). For incident CAC, those without baseline CAC at the year 15 examination ($n = 2,062$) were included for that analysis.

FG Measurement

FG was measured in nonpregnant participants who reported fasting ≥ 8 h at years 15, 20, and 25. FG was assayed using hexokinase coupled to glucose-6-phosphate dehydrogenase (Linco Research, St Louis, MO). Quality control using a commercially purchased pool of control subjects showed that within-run precision and between-run precision is $<1\%$ and $<2\%$ coefficient of variation (CV), respectively (15). The data were recalibrated to standardize serum glucose values across CARDIA examinations.

Covariate Ascertainment

Standardized questionnaires and protocols were used to collect data on participant demographic characteristics, smoking, alcohol, physical activity, medical history, and use of medications (14). Height and weight were measured without shoes and in light clothing and were used to calculate BMI (weight in kilograms divided by the square of height in meters). Blood pressure (BP) was measured in triplicate after a 5-min rest using either a random-zero mercury sphygmomanometer (examination year 15) or an automated oscillometer (examination years 20 and 25) (model HEM907XL; OMRON). Values from the oscillometer were calibrated to the sphygmomanometric measures across examinations. BP was determined as the mean of the second and third measurements (16). Other laboratory measures, such as serum creatinine, total cholesterol, and LDL cholesterol (LDL-C), were collected for analysis.

CAC Assessment

CAC was assessed using electron beam computed tomography (Chicago and Oakland centers at years 15 and 20) or multidetector computed tomography scanners (Birmingham and Minneapolis centers at years 15 and 20 and all centers at year 25). A standardized protocol for the CAC assessment process has previously

been described in detail (17). Contiguous 3-mm-thick slices from the root of the aorta to the apex of the heart were obtained. Image data were transmitted electronically to the CARDIA Reading Center, and a trained technician blinded to participant characteristics identified a region of interest for each potential foci of CAC. A calcium score in Agatston units was calculated for each calcified lesion, and scores from the four major coronary arteries (left main, left circumflex, left anterior descending, and right coronary) were summed to compute a total calcium score (18). All image data were analyzed with high between-reader and within-reader reproducibility (17).

Statistical Analysis

Continuous variables are described as mean (SD) for normally distributed data or median (range) for nonnormally distributed data. Categorical variables are reported as frequency (percentage). The main parameters of intraindividual FG variability were calculated for each participant between three successive FG measurements: the SD of FG (FG-SD), the CV of the mean FG (FG-CV), and the average real variability (ARV) of FG (FG-ARV). An FG variability formula has previously been published for CARDIA (15). CAC progression was computed for each individual as the difference of logarithmic CAC scores at follow-up and baseline ($\log[\text{CAC (follow-up)} + 1] - \log[\text{CAC (baseline)} + 1]$) (19). According to this approach, CAC progression was normally distributed. CAC progression was defined as 1) incident CAC with increase >0 Agatston units at last follow-up examination (year 25) among those with CAC = 0 at baseline (year 15) and 2) any CAC progression with increase >0 Agatston units until last follow-up examination (year 25).

Missing covariate values were generated using a fully conditional specification multiple imputation method (20,21). The percentage of missing data before imputation was 1.4% for smoking, 1.1% for LDL-C, 0.8% for alcohol, and $<0.2\%$ for other covariates. Linear regression analysis was performed to estimate unadjusted and multivariable-adjusted association between a 1-SD increment for continuous FG-SD, FG-CV, and FG-ARV with CAC progression using the following models: 1) unadjusted; 2) adjusted for

age, sex, and race; 3) adjusted for variables in model 2 plus cumulative risk factors such as BMI, current smoker status, milliliters of daily alcohol consumption, systolic blood pressure (SBP), antihypertensive medication use, physical activity, serum creatinine, total cholesterol, and LDL-C; and 4) adjusted for variables in model 3 plus average FG level and FG level change during variability measurement. To confirm whether the FG variability–CAC progression association is independent of FG increment during follow-up, we further analyzed separate

models with adjustment for 1) incidence of diabetes and diabetes medication use during variability measurement and 2) FG level at the time of CAC assessment at year 25. We also included adjustment for baseline CAC for any CAC progression. To evaluate the potential influence of incident diabetes during variability measurement, we further investigated the association of FG variability with CAC progression stratified by diabetes status at the time of CAC assessment at year 25. A two-sided P value <0.05 was considered statistically significant. All analyses

were conducted using SPSS, version 20 (SPSS, Chicago, IL).

RESULTS

Demographic and clinical characteristics of study participants according to quartile of FG-CV are presented in Table 1. The baseline FG level was not gradually increased with quartiles of FG-CV. Conversely, greater changes in FG, FG-SD, FG-ARV, and incidence of diabetes were associated with higher FG-CV during 10 years (all $P < 0.001$). Changes over time for other cardiovascular risk factors

Table 1—Baseline characteristics of 2,256 participants by quartile of FG-CV from 2000–2001 to 2010–2011

	FG-CV (%)				P^*
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
<i>N</i>	563	564	566	563	
Age at Y15 (years), mean (SD)	40.7 (3.5)	40.2 (3.5)	40.4 (3.6)	40.5 (3.6)	0.148
Sex, <i>n</i> (% male)	252 (44.7)	244 (43.3)	250 (44.2)	253 (44.9)	0.949
Race, <i>n</i> (% Black)	202 (35.8)	232 (41.1)	237 (41.9)	304 (54.0)	<0.001
BMI at Y15 (kg/m^2), mean (SD)	28.0 (5.8)	28.1 (5.8)	27.9 (5.6)	30.0 (6.6)	<0.001
BMI at Y25 (kg/m^2), mean (SD)	29.2 (6.4)	29.3 (6.0)	29.3 (6.0)	31.7 (7.1)	<0.001
Current smoker at Y15, <i>n</i> (%)	97 (17.2)	102 (18.1)	98 (17.3)	143 (25.4)	0.001
Current smoker at Y25, <i>n</i> (%)	79 (14.0)	79 (14.0)	77 (13.6)	103 (18.3)	0.164
Alcohol consumption at Y15 (mL/day), mean (SD)	9.9 (21.0)	10.6 (20.6)	10.9 (20.4)	11.5 (22.3)	0.638
Alcohol consumption at Y25 (mL/day), mean (SD)	12.5 (24.7)	11.4 (18.8)	11.3 (18.3)	12.1 (21.5)	0.738
SBP at Y15 (mmHg), mean (SD)	111.5 (14.2)	111.1 (12.8)	111.2 (12.7)	116.9 (16.4)	<0.001
SBP at Y25 (mmHg), mean (SD)	118.3 (15.2)	117.7 (15.8)	118.7 (14.6)	123.1 (18.0)	<0.001
BP medication use at Y15, <i>n</i> (%)	32 (5.7)	28 (5.0)	33 (5.8)	63 (11.2)	<0.001
BP medication use at Y25, <i>n</i> (%)	117 (20.7)	133 (23.6)	132 (23.3)	238 (42.3)	<0.001
Physical activity at Y15 (exercise units), mean (SD)	348.2 (274.3)	361.1 (268.1)	359.0 (294.1)	332.6 (281.6)	0.300
Physical activity at Y25 (exercise units), mean (SD)	350.4 (284.8)	353.2 (269.6)	345.0 (283.9)	305.1 (264.3)	0.011
Serum creatinine at Y15 (mg/dL), mean (SD)	0.97 (0.16)	1.00 (0.32)	0.98 (0.17)	0.99 (0.30)	0.122
Serum creatinine at Y25 (mg/dL), mean (SD)	0.87 (0.18)	0.88 (0.24)	0.88 (0.52)	0.88 (0.37)	0.924
Total cholesterol at Y15 (mg/dL), mean (SD)	186.1 (33.6)	184.1 (33.4)	185.7 (34.7)	186.0 (35.9)	0.729
Total cholesterol at Y25 (mg/dL), mean (SD)	193.6 (35.0)	193.6 (36.8)	194.2 (36.1)	191.6 (38.0)	0.648
LDL-C at Y15 (mg/dL), mean (SD)	114.6 (30.2)	112.8 (31.7)	114.5 (32.1)	113.1 (31.4)	0.701
LDL-C at Y25 (mg/dL), mean (SD)	113.1 (30.3)	112.6 (33.4)	114.3 (32.0)	110.2 (34.0)	0.202
FG at Y15 (mg/dL), mean (SD)	87.8 (7.7)	84.7 (8.7)	81.6 (9.9)	89.8 (32.0)	<0.001
FG at Y20 (mg/dL), mean (SD)	91.1 (7.6)	92.8 (9.1)	94.9 (10.9)	113.6 (46.6)	<0.001
FG at Y25 (mg/dL), mean (SD)	90.9 (7.8)	92.7 (9.8)	94.7 (11.1)	121.3 (50.6)	<0.001
Change in FG (mg/dL), mean (SD)	4.5 (2.8)	9.4 (3.8)	13.9 (5.3)	40.5 (43.0)	<0.001
Incident diabetes by Y25, <i>n</i> (%)	13 (2.3)	13 (2.3)	21 (3.7)	101 (17.9)	<0.001
FG variability					
FG-SD (mg/dL), mean (SD)	3.4 (1.2)	6.4 (1.0)	9.4 (1.4)	26.6 (25.7)	<0.001
FG-CV (%), mean (SD)	3.8 (1.3)	7.2 (0.9)	10.4 (1.1)	21.9 (12.4)	<0.001
FG-ARV (mg/dL per year), mean (SD)	4.2 (1.9)	7.6 (2.1)	11.0 (2.8)	30.5 (32.3)	<0.001
CAC Agatston score at Y15, median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.656
CAC Agatston score at Y25, median (Q1–Q3)	0 (0–2.3)	0 (0–2.2)	0 (0–3.7)	0 (0–18.7)	0.002
CAC volume (mm^3) at Y15, median (Q1–Q3)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.222
CAC volume (mm^3) at Y25, median (Q1–Q3)	0 (0–2.4)	0 (0–1.7)	0 (0–3.4)	0 (0–15.7)	0.002
Any CAC present at Y15, <i>n</i> (%)	45 (8.0)	50 (8.9)	44 (7.8)	55 (9.8)	0.618
Any CAC present at Y25, <i>n</i> (%)	150 (26.6)	149 (26.4)	162 (28.6)	197 (35.0)	0.004

Q, quartile; Y, year. P value for global test: ANOVA for continuous variables and Pearson χ^2 tests for categorical variables.

such as increasing BMI, systolic BP, and use of BP-lowering medications were associated with higher FG-CV (all $P < 0.001$). However, age, sex, alcohol consumption, serum creatinine, and cholesterol levels were not significantly different according to quartile of FG-CV. Findings were similar between these characteristics with FG-SD and FG-ARV during 10 years.

CAC progression among participants during 10 years is shown in Supplementary Fig. 2. Participants with baseline CAC at the year 15 examination experienced faster progression of CAC compared with those without baseline CAC (mild CAC progression, 19.3% vs. 31.4%; moderate CAC progression, 3.0% vs. 45.4%; and severe CAC progression, 0.2% vs. 23.2%). Furthermore, CAC progression was stratified by the quartile of FG-CV (Fig. 1). Findings showed that no significant difference in CAC score was observed at baseline (at year 15); however, after the 5-year follow-up, CAC scores presented a significant difference according to quartile of FG-CV (Q1 vs. Q4, $P = 0.030$) and further increased at year 25 (Q1 vs. Q4, $P < 0.001$). Similar trends were also observed in FG-SD and FG-ARV (Supplementary Fig. 3). Taken together, CAC progression was gradually increased with quartiles of FG variability during the 10-year follow-up.

The unadjusted and adjusted effect estimates for the association of FG-CV with CAC progression are shown in Table 2. At year 25, a 1-SD increment in FG-CV showed significant association with progression of CAC as demonstrated as percent change in (CAC + 1), with incident CAC 9.1% (95% CI 6.3, 11.8) and any CAC progression 9.5% (95% CI 6.9, 12.0) after adjustment for demographics (Table 2, model 2), but this association was attenuated after additional adjustment for cumulative risk factors (Table 2, model 3). Additionally, we observed the association for 1-SD increment in FG-CV across all test results for the final model, model 4, including adjustment for average of FG and change in FG level during variability measurement: incident CAC 5.9% (95% CI 1.0, 10.7) and any CAC progression 6.7% (95% CI 2.3, 11.1). The associations between FG-CV with the incident CAC and any CAC progression remained significant after further adjustment for the incidence of diabetes, diabetes medication use (Table 2, model 4A), FG level at year 25 (Table 2, model

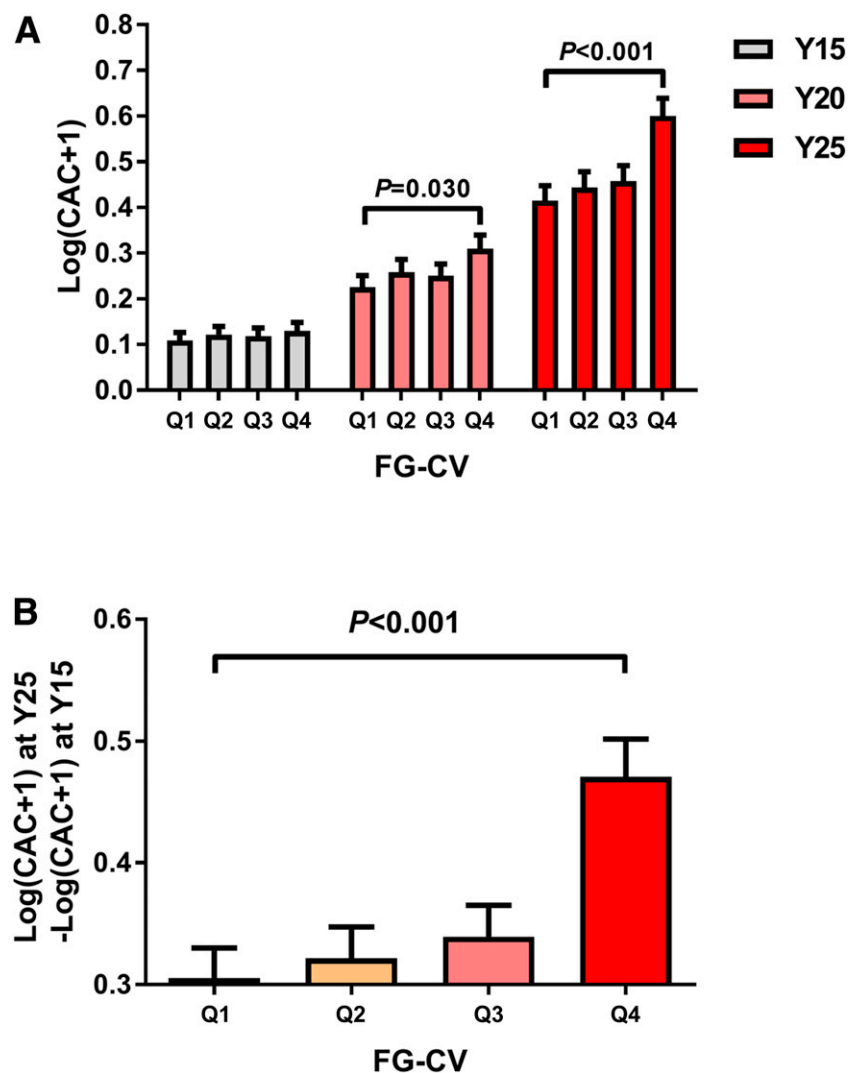


Figure 1—CAC progression according to the quartile of FG-CV A: CAC score at baseline (year 15), 5-year (year 20), and 10-year (year 25) follow-up. B: CAC progression gradually increased with quartiles of FG-CV during the 10-year follow-up. Q, quartile; Y, year.

4B), and baseline CAC (Table 2, model 4C). A depiction of FG-CV with CAC progression during 10 years is presented in Supplementary Fig. 4. Similar patterns of association between CAC progression with FG-SD and FG-ARV were also observed (Supplementary Tables 1 and 2). Besides, findings were similar between FG variability and CAC progression when we used volume of CAC to estimate CAC progression (Supplementary Tables 3–5).

The associations of FG-CV with the incident CAC and any CAC progression during the 10-year follow-up were stronger among subjects without diabetes than for subjects with diabetes (Supplementary Table 6). This disparate strength of association by diabetes status was not

statistically significant (all P for interaction by diabetes status > 0.1). Additionally, neither incident CAC nor any CAC progression was associated with FG-CV among subjects with diabetes after further adjustment for cumulative risk factors, average of FG, and change in FG level during variability measurement. Among subjects without diabetes, however, these associations remained significantly associated (Fig. 2). Similar patterns of association of CAC progression with FG-SD and FG-ARV were also observed stratified by diabetes status. Of note, both FG-SD and FG-ARV were associated with CAC progression among subjects without diabetes even after adjustment for average of FG and change in FG level. A depiction of FG-SD and FG-ARV

Table 2—Multivariable association of a 1-SD increase in FG-CV with CAC progression over 10 years among individuals in CARDIA

Model	% CAC progression per 1-SD increase in FG-CV (95% CI)	P
Incident CAC (>0 Agatston units), N = 2,062*		
Model 1	9.3 (6.5, 12.1)	<0.001
Model 2	9.1 (6.3, 11.8)	<0.001
Model 3	6.7 (4.0, 9.4)	<0.001
Model 4	5.9 (1.0, 10.7)	0.028
Model 4A	5.3 (0.0, 10.5)	0.049
Model 4B	5.9 (1.1, 10.6)	0.028
Any CAC progression (>0 Agatston units), N = 2,256†		
Model 1	9.6 (6.9, 12.2)	<0.001
Model 2	9.5 (6.9, 12.0)	<0.001
Model 3	6.8 (4.3, 9.3)	<0.001
Model 4	6.7 (2.3, 11.1)	0.004
Model 4A	6.0 (1.5, 10.6)	0.012
Model 4B	6.8 (2.3, 11.4)	0.004
Model 4C	6.8 (2.2, 11.4)	0.004

A 1-SD unit increment in FG-CV is 9.3%. Model 1, no adjustment; model 2, adjustment for age, sex, and race; model 3, adjustment for variables in model 2 plus BMI, current smoker status (yes/no), milliliters of daily alcohol consumption, SBP, antihypertensive medication use (yes/no), physical activity, serum creatinine, total cholesterol, and LDL-C; model 4, adjustment for variables in model 3 plus average of FG and change in FG level during variability measurement; model 4A, adjustment for variables in model 4 plus incidence of diabetes and diabetes medication use; model 4B, adjustment for variables in model 4 plus FG level at year 25; model 4C, for individuals with any CAC progression, adjustment for variables in model 4 plus baseline CAC. *Evaluated only among individuals without baseline CAC at the year 15 examination. †CAC progression was calculated as the difference of logarithmic CAC score at follow-up and baseline ($\log[\text{CAC}(\text{follow-up}) + 1] - \log[\text{CAC}(\text{baseline}) + 1]$).

with CAC progression at year 25 is presented in Supplementary Figs. 5 and 6. Subgroup analysis showed no significant difference stratified by sex category (all *P* for interaction >0.1) (Supplementary Table 7), but stronger association of FG-SD or FG-ARV with incident CAC and any CAC progression was observed in the White subgroup (*P* for interaction <0.05) (Supplementary Table 8).

CONCLUSIONS

In this prospective cohort study with 10 years of follow-up, we demonstrate for the first time that greater FG variability during young adulthood was independently associated with greater CAC progression by middle age. This association was observed after adjustment for demographic and cardiovascular risk factors, average FG level, change in FG level during variability measurement, diabetes incidence, and medication use. We also show that FG variability, as determined by CV, SD, and ARV, was more strongly associated with CAC progression in subjects without diabetes than in those with diabetes. This was possibly

attributable to the use of diabetes medication and the development of diabetes weakening the association between glycemic variability and CAC progression. Subjects with diabetes experience greater CAC progression than those without diabetes (22). In addition, diabetes medication use disrupts the natural course of glycemic variability and may alter any association of glycemic variability with CAC progression (23,24).

Several potential pathophysiological mechanisms may contribute to the association between glycemic variability and CAC progression. Firstly, greater glycemic fluctuation has been shown to induce overproduction of superoxide, reduce nitric oxide availability, trigger activation of monocytes and macrophages, and increase inflammatory cytokine generation, which result in endothelial damage and vascular remodeling (25–29). These changes on vascular structure and function are common findings in CAC development. Secondly, transient hyperglycemia may induce alkaline phosphatase activation and osteogenic changes in vascular smooth muscle cells, which

are involved in the onset or progression of CAC (30). Thirdly, greater long-term glycemic variability may induce cellular metabolic memory and increase insulin resistance (31), and these processes may contribute to the increased risk of CAC (32). Lastly, increased glycemic variability may be a marker of poor quality of life, lack of social support, and other comorbidities (33). Consistent with previous studies, we found that individuals with greater FG variability tend to be less physically active and had higher BMI and SBP.

Emerging evidence demonstrates that glycemic variability may be an important predictor of stroke, retinopathy, and other cardiovascular complications among older individuals with diabetes (12,13,31). However, few studies have specifically investigated the relationship between FG variability and CAC (a predictor of macrovascular complications) in young adults and adults in early middle age. Prior epidemiological and clinical studies of glycaemia and CAC have reported conflicting results. No association between impaired FG and CAC was reported after adjustment for confounding factors in the Framingham Heart Study (34). In contrast, findings from the Heinz Nixdorf Recall Study showed significant association between impaired FG and CAC (35). In CARDIA, higher HbA_{1c} was also associated with advanced CAC progression (36). HbA_{1c} level reflects average glucose over a period of 8–12 weeks, but it fails to capture real-time glycemic fluctuation (37). Recent evidence indicated that long-term visit-to-visit FG variability was a better predictor than mean HbA_{1c} for assessing the risk of future development of micro- and macrovascular complications (31). Moreover, results from the Veterans Affairs Diabetes Trial showed that variability of FG other than HbA_{1c} level was associated with cardiovascular disease after adjustment for multiple baseline covariates, suggesting that FG variability may be a more sensitive indicator in regard to potential cardiovascular complications (11). Therefore, it is important to elucidate the association between glycemic variability and CAC development. In the current study, we define long-term glycemic variability by estimating CV, SD, and ARV for FG and provide further

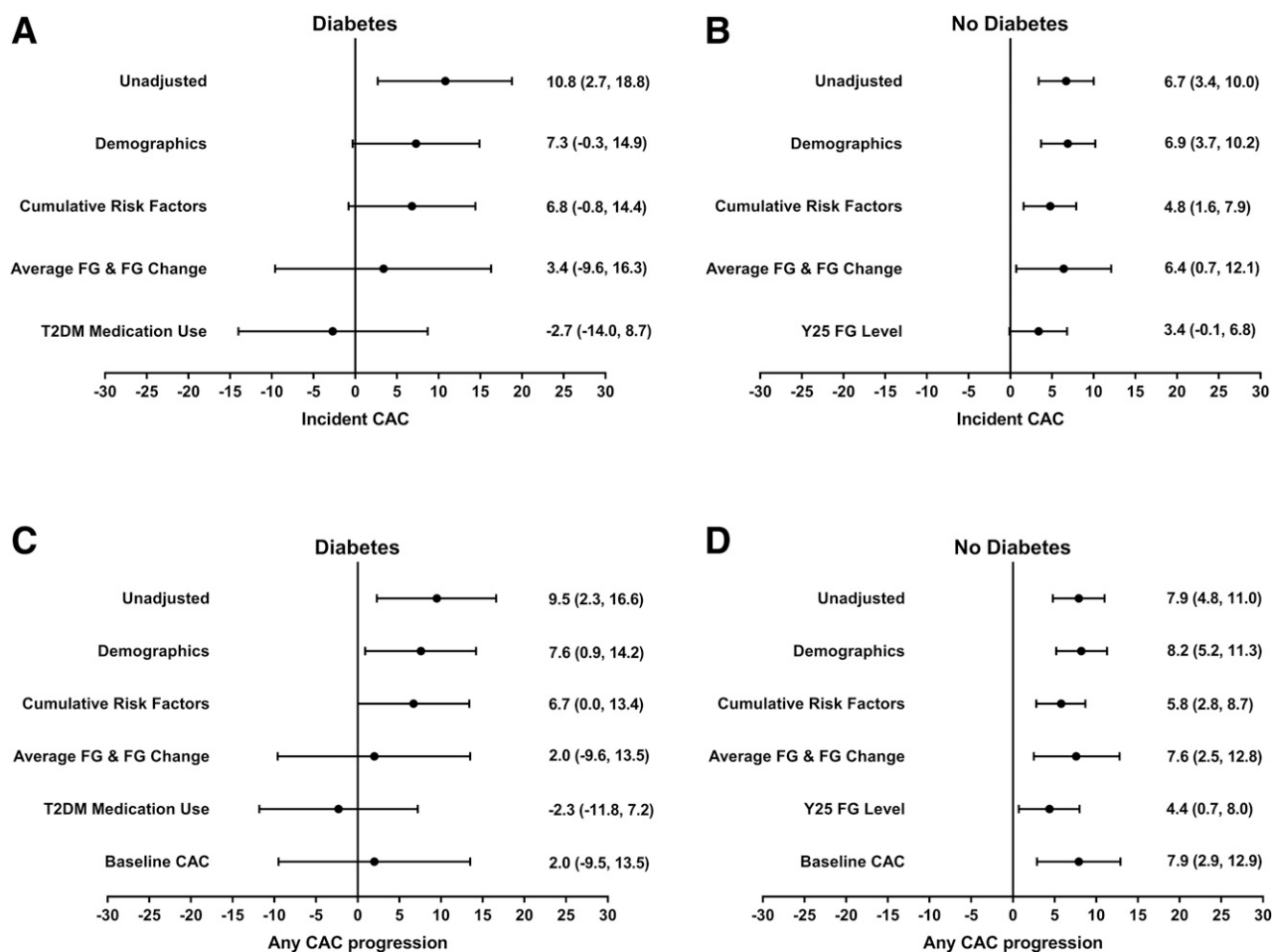


Figure 2—Forest plot of the association between a 1-SD unit increment in FG-CV and percent progression of incident CAC among individuals with diabetes (A) or without diabetes (B) and any CAC progression among individuals with diabetes (C) or without diabetes (D). Model adjustment: demographics—age, sex, and race; cumulative risk factors—demographics plus BMI, current smoker status, milliliters of daily alcohol consumption, SBP, antihypertensive medication use, physical activity, serum creatinine, total cholesterol, and LDL-C; average FG & FG change—cumulative risk factors plus average FG level and change in FG level during variability measurement; T2DM medication use—average FG & FG change plus use of medication for type 2 diabetes; Y25 FG level—average FG & FG change plus FG level at year 25; baseline CAC—average FG & FG change plus baseline CAC.

evidence that greater FG variability during young adulthood leads to greater CAC progression by middle age.

The strengths of our study include its status as a prospective study related to subclinical coronary artery disease among young adults and adults in early middle age during 10 years of follow-up and the relatively large sample size, standardized data collection protocols, and rigorous quality control. Some potential limitations should be considered. Assessment of CAC began at the year 15 examination, so participants were not included in these analyses due to missing CAC score at years 15 and 25. Exclusion of these participants may have affected our findings, but the retention of CARDIA participants remained high. Interscan variability may have a potential effect on the change of CAC scores, but previous studies in

CARDIA showed high between-reader and within-reader reproducibility (17,38). FG measures were collected every 5 years and may not reflect daily glucose fluctuation, traditionally assessed among individuals. HbA_{1c} and 2-h glucose levels were not measured frequently enough during CARDIA follow-up to estimate variability for these measures and their association with CAC progression. Lastly, this was an observational study, and other potential residual and unknown confounding variables may be present.

In conclusion, we observed that greater individual variability in FG during young adulthood was associated with greater CAC progression by middle age. These results suggest that efforts to achieve normal consistent levels of glucose very early in life may reduce the risk for future

CAC and other subclinical coronary artery diseases.

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Author Contributions. W.F., C.O., F.H., and M.C. conceived the research idea and conducted the analysis. W.F., C.O., and F.H. analyzed and interpreted the data. M.C. advised on statistical analysis methods. W.F. drafted the manuscript. Z.L., W.G., X.F., F.Z., and K.Z. contributed to the discussion. W.F., Z.L., C.O., F.H., and M.C. provided critical revision of the manuscript for important intellectual content. W.F., Z.L., W.G., X.F., F.Z., K.Z., C.O., F.H., and M.C. reviewed and approved the final manuscript. M.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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